CLAIMS

We claim:

1. A crystallizable composition comprising an HCV NS3 helicase protein and an oligonucleotide.

2. The composition according to claim 1, wherein said HCV NS3 helicase comprises amino acids 167-631 of SEQ ID NO:1 and wherein said oligonucleotide is a single stranded polynucleotide of between 6 and 12 nucleotides in length.

3. A crystallized complex comprising an HCV NS3 helicase protein and an oligonucleotide.

4. The crystallized complex according to claim 3, wherein said oligonucleotide is a single stranded polynucleotide of between 6 and 12 nucleotides in length.

5. A method of producing a crystallized complex comprising an HCV NS3 helicase and an oligonucleotide comprising the steps of:

a. obtaining a crystallizable composition comprising an NS3 helicase protein and an oligonucleotide in a molar ratio of between 1:5 and 5:1; and

b. subjecting said composition to conditions which promote crystallization.

6. The method according to claim 5, wherein said HCV NS3 helicase comprises amino acids 167-631 of SEQ ID NO:1 and wherein said oligonucleotide is a single stranded polynucleotide of between 6 and 12 nucleotides in length.

7. A computer for producing a three-dimensional representation of:

a. a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding pocket defined by structure coordinates of NS3 amino acids Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501 and Tyr502 according to Figure 1; or

b. a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from

the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

(i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of NS3 amino acids Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501 and Tyr502 according to Figure 1;

(ii) a working memory for storing instructions for processing said machine-readable data;

(iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

8. The computer according to claim 7, wherein said computer produces a three-dimensional representation of:

a) a molecule or molecular complex comprising a binding pocket defined by the structure coordinates of NS3 helicase amino acids Val232, Thr254,

Gly255, Thr269, Gly271, Lys272, Ala275, Trp501, Tyr502, Pro230, Val256, Thr298, Ala497, Lys551, Gln552, Gly554, Glu555, Asn556 and Pro558, according to Figure 1; or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å; and

wherein said machine readable data comprises the structure coordinates of NS3 amino acids Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501, Tyr502, Pro230, Val256, Thr298, Ala497, Lys551, Gln552, Gly554, Glu555, Asn556 and Pro558, according to Figure 1.

9. A computer for producing a three-dimensional representation of:

a) a molecule or molecular complex comprising a binding pocket defined by the structure coordinates of NS3 helicase amino acids His369, Ser370, Lys371, Tyr392, Arg393, Thr411, Asp412, Ala413, Cys431, Val432, Gln434, Ile446, Thr448, Arg461, Glu493, Glu555, Asn556 and Phe557, according to Figure 1; or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a

binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

(i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of NS3 amino acids His369, Ser370, Lys371, Tyr392, Arg393, Thr411, Asp412, Ala413, Cys431, Val432, Gln434, Ile446, Thr448, Arg461, Glu493, Glu555, Asn556 and Phe557, according to Figure 1;

(ii) a working memory for storing instructions for processing said machine-readable data;

(iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

10. A computer for producing a three-dimensional representation of:

a) a molecule or molecular complex comprising a binding pocket defined by the structure

coordinates of NS3 helicase amino acids Pro205, Thr206, Gly207, Ser208, Gly209, Lys210, Ser211, Thr212, Lys213, Asn229, Ala234, Gly237, Phe238, Tyr241, Asp290, Glu291, His293, Thr322, Ala323, Thr324, Gln460, Gly463, Arg464 and Arg467, according to Figure 1; or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, wherein said computer comprises:

(i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of NS3 amino acids Pro205, Thr206, Gly207, Ser208, Gly209, Lys210, Ser211, Thr212, Lys213, Asn229, Ala234, Gly237, Phe238, Tyr241, Asp290, Glu291, His293, Thr322, Ala323, Thr324, Gln460, Gly463, Arg464 and Arg467, according to Figure 1;

(ii) a working memory for storing instructions for processing said machine-readable data;

(iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

11. The computer according to any one of claims 7 to 10, wherein said computer produces a three-dimensional representation of:

a. a molecule or molecular complex defined by structure coordinates of all of the NS3 helicase amino acids set forth in Figure 1, or

b. a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å; and

wherein said machine readable data contains the coordinates of all of the NS3 helicase amino acids set forth in Figure 1.

12. A computer for determining at least a portion of the structure coordinates corresponding to X-ray diffraction data obtained from a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage

medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates of NS3 helicase according to Figure 1;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises X-ray diffraction data obtained from said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

13. The computer according to claim 12, wherein said molecule or molecular complex comprises a

polypeptide having helicase activity.

14. A method for evaluating the potential of a chemical entity to associate with:

a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of NS3 helicase amino acids Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501 and Tyr502 according to Figure 1, or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Δ comprising the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and

ii) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket.

15. The method according to claim 14, wherein said method evaluates the potential of a chemical entity to associate with:

a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of NS3 helicase amino acids Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501, Tyr502, Pro230, Val256, Thr298, Ala497, Lys551, Gln552, Gly554, Glu555, Asn556 and Pro558 according to Figure 1, or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

16. A method for evaluating the potential of a chemical entity to associate with:

a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of NS3 helicase amino acids His369, Ser370, Lys371, Tyr392, Arg393, Thr411, Asp412, Ala413, Cys431, Val432, Gln434, Ile446, Thr448, Arg461, Glu493, Glu555, Asn556 and Phe557 according to Figure 1, or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than

1.5 Å comprising the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and

ii) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket.

17. A method for evaluating the potential of a chemical entity to associate with:

a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of NS3 helicase amino acids Pro205, Thr206, Gly207, Ser208, Gly209, Lys210, Ser211, Thr212, Lys213, Asn229, Ala234, Gly237, Phe238, Tyr241, Asp290, Glu291, His293, Thr322, Ala323, Thr324, Gln460, Gly463, Arg464 and Arg467 according to Figure 1, or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å comprising the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a

binding pocket of the molecule or molecular complex; and

ii) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket.

18. The method according to any one of claims 14 to 17, wherein said method evaluates the potential of a chemical entity to associate with a molecule or molecular complex:

a. defined by structure coordinates of all of the NS3 helicase amino acids, as set forth in Figure 1, or

b. a homologue of said molecule or molecular complex having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

19. A method for identifying a potential agonist or antagonist of a molecule comprising a NS3 helicase U8-like binding pocket comprising the steps of:

a. using the atomic coordinates of Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501 and Tyr502 according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino

acids of not more than 1.5Å, to generate a three-dimensional structure of molecule comprising a NS3 helicase U8-like binding pocket;

b. employing said three-dimensional structure to design or select said potential agonist or antagonist;

c. synthesizing said agonist or antagonist; and

d. contacting said agonist or antagonist with said molecule to determine the ability of said potential agonist or antagonist to interact with said molecule.

20. The method according to claim 19, wherein the atomic coordinates used in step a. comprise Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501, Tyr502, Pro230, Val256, Thr298, Ala497, Lys551, Gln552, Gly554, Glu555, Asn556 and Pro558 according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

21. A method for identifying a potential agonist or antagonist of a molecule comprising a NS3 helicase U4-like binding pocket comprising the steps of:

a. using the atomic coordinates of His369, Ser370, Lys371, Tyr392, Arg393, Thr411, Asp412, Ala413, Cys431, Val432, Gln434, Ile446, Thr448, Arg461, Glu493, Glu555, Asn556 and Phe557 according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, to generate a three-dimensional structure of molecule comprising a NS3 helicase ~~03~~ U4-like binding pocket;

b. employing said three-dimensional structure to design or select said potential agonist or antagonist;

c. synthesizing said agonist or antagonist; and

d. contacting said agonist or antagonist with said molecule to determine the ability of said potential agonist or antagonist to interact with said molecule.

22. A method for identifying a potential agonist or antagonist of a molecule comprising a NS3 helicase ATP-like binding pocket comprising the steps of:

a. using the atomic coordinates of Pro205, Thr206, Gly207, Ser208, Gly209, Lys210, Ser211, Thr212, Lys213, Asn229, Ala234, Gly237, Phe238, Tyr241,

Asp290, Glu291, His293, Thr322, Ala323, Thr324, Gln460, Gly463, Arg464 and Arg467 according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, to generate a three-dimensional structure of molecule comprising a NS3 helicase NTP-like binding pocket;

b. employing said three-dimensional structure to design or select said potential agonist or antagonist;

c. synthesizing said agonist or antagonist; and

d. contacting said agonist or antagonist with said molecule to determine the ability of said potential agonist or antagonist to interact with said molecule.

23. The method according to any one of claims 19 to 22, wherein in step a., the atomic coordinates of all the amino acids of NS3 helicase according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å are used.

24. A method of obtaining structural information about a molecule or molecular complex whose structure is unknown comprising the steps of:

a) crystallizing said molecule or molecular complex of unknown structure;

b) generating X-ray diffraction data from said crystallized molecule or molecular complex; and

c) applying at least a portion of the structure coordinates set forth in Figure 1 to the X-ray diffraction data to generate a three-dimensional electron density map of the molecule or molecular complex whose structure is unknown.